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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

CANELLA, KAREN A

ART UNIT PAPER NUMBER

1643

DATE MAILED: 10/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/760,119	Applicant(s) BACUS, SARAH S.	
	Examiner Karen A. Canella	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1,2 and 4-6 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) 1,2 and 4-6 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>Apr 5, 2005</u> . | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

1. Claim 1 has been amended. Claim 3 has been canceled. Claims 1, 2 and 4-6 are pending and under consideration.

2. Acknowledgment is made of applicant claim to an earlier effective filing date through provisional applications 60/176,514 and 60/176,515. Upon review of each of these applications, it is noted that p21 and SA-B-gal were described as senescence associated marker of the invention, no markers of apoptosis of differentiation were described as part of the inventions and no mention was made of p27, p16 or TGF-beta as a senescence associated, apoptotic of differentiation associated marker of the invention. It is concluded that the provisional applications fails to provide an adequate written description of the instant invention with respect to the markers of p27, p16 or TGF-beta, and thus, the effective priority date will be the instant filing date of January 12, 2001.

3. Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "multiplicity of stains" in claim 6 lacks antecedent basis in claim 5.

4. Claims 1, 2 and 4-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

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Claim 1 is drawn to a method for determining a response to administration of a chemotherapeutic or chemopreventative agent comprising collecting a first tissue or cell sample from an individual before exposing the individual to the chemotherapeutic or chemopreventative agent; collecting a second tissue or cell sample from the individual after exposing the individual to the chemotherapeutic or chemopreventative agent; immunohistochemically staining the first and the second tissue or cell samples using a detectably labeled antibody directed against a biological marker associated with terminal differentiation, wherein the biological marker is p21, p27, p16, TGF-beta or SA-Beta-Gal; measuring the optical density of the stained cells of step (c) wherein the stained cells are illuminated with light having a wavelength absorbed by the stain; determining whether expression of the biological marker associated with apoptosis was increased following exposure to the chemotherapeutic or chemopreventative agent. Claim 2 embodies the method of claim 1 wherein the detectable label is a chromogen or fluorophore. Claim 5 embodies the method of claim 1 wherein the optical density of the stained cells is preformed by image analysis. Claim 6 embodies the method of claim 5 wherein the image analysis is preformed by splitting a signal comprising the optical density of the stained cells into a multiplicity of signals that are processed using optical filters having different absorption and transmittance properties, so that each signal is specific for one of a multiplicity of stains used to stain the cells.

(A) As drawn to "tissue or cell samples" and the lack of correlation between TGF-beta, p21, p16 and p27 with the states of apoptosis, terminal differentiation and senescence within said "tissue or cell samples" treated by a chemotherapeutic agent.

The instant claims are drawn to a method of determining a response to administration of a chemotherapeutic or chemopreventative agents to an individual comprising determining whether expression of a biological marker associated with senescence, apoptosis or terminal differentiation was increased in a tissue or cellular sample taken from the individual following exposure to said chemotherapeutic or chemopreventative agent, wherein said biological marker includes p21, p27, p16, TGF-beta and SA-B-gal. The claims are broadly drawn to encompass any tissue sample including normal tissues and cells, as well as samples comprising diseased tissues or cells, wherein said diseased tissues or cells result from infectious agents, autoimmune diseases, genetically inherited diseases and cancers of all type including solid tumors and

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hematopoietic cancers. The specification states that "In the use of anticancer drugs, monoclonal antibodies, or chemopreventative agents, growth arrest, terminal differentiation and cell death of the cancerous or precancerous cells is intended". However, this does not serve to limit the scope of the claims to taking a sample of cancerous tissue or cells from an individual but encompasses a taking a sample of tissue or cells from a multitude of diseased and normal tissues and cells, and exposure to said tissues and cells to any chemotherapeutic and chemopreventative agents. The art teaches that the relationship between the expression of p16, p21, p27 and TGF-beta and the state of differentiation, apoptosis and chemotherapy is complex. For instance, Morris et al (Biochemical and Molecular Medicine, 1997, Vol. 60, pp. 108-115), teach that treatment of Raji lymphoma in vivo with methylprednisolone causes a reduction in the level of tumor growth, however, no change in the level of TGF-beta was observed and CDKN1 (p21) was decreased rather than increased as required by the instant method. The abstract of Sethi et al (Proc Annu Meet Am Soc Clin Oncol, 1996, Vol. 15, pp. A1308) teaches that the expression of Bcl2 in lymphomas confounds the apoptosis inducing effect of TGF-beta thus detection of an increase in TGF-beta by a lymphoma cell that concurrently over expressed Bcl2 would not be expected to be indicative of apoptosis. Urashima et al (Blood, 1997, Vol. 90, pp. 4106-4115) teach that the p16 gene is frequently deleted in lymphoblastic leukemia associated with the growth of less differentiated tumor cells. Although the abstract teaches that ectopic expression of p16 in the p16-negative cells suppresses cell growth, the specification provides no teaching regarding how the level of p16 is to be increased as a result of chemotherapy in a sample of leukemia cells having a deleted p16 gene. The specification fails to provide objective evidence that apoptotic cells would exhibit an increased expression of p16 relative to the same cell in the non-apoptotic state. Further Wang et al (International Journal of Oncology, 1999, Vol. 15, pp. 1097-1102) teach that cisplatin induced a senescence-type growth arrest in human tumor cell lines without an alteration in the level of either p16 or p21.

In order to use the expression of p21, p16, TGF-beta or p27 as a marker of apoptotic cells resulting from a chemotherapeutic agent, it would be necessary to assay for said marker within a specific time period after the administration of said chemotherapeutic agent to a patient in need thereof. Li et al (Leukemia and Lymphoma, 1994, Vol. 13, suppl. 1, pp. 65-70) teach that apoptosis of leukemic cells was seen between 8 to 24 hrs after the administration of DNA

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topoisomerase inhibitors but 48-72 hours after the administration of Taxol or Ara-C. However, the instant claims encompass the analysis of cells taken from individuals which are not limited to cancer cells or to leukemic cells, and the administration of chemotherapeutic agents which are not limited to topoisomerase inhibitors, taxol or Ara-C or other anti-leukemic agents. It is the nature of apoptotic cells that they disintegrate into small pieces and are eliminated by the phagocytic cells of the immune system. It would be necessary to first determine the time frame of apoptosis induction by means of observing DNA strand breaks before proceeding to determine if TGF-beta, p21, p16 or p27 was thereby increased for any sample of tissue or cells taken from an individual who had received any chemotherapeutic agent. This would be further complicated by the fact that if the dosage of the chemotherapeutic agent was insufficient or the cells were resistant to said chemotherapeutic agent, apoptosis would not be in evidence (the abstract of Cen et al, *Zhonghua nei ke za zhi* [Chinese Journal of Internal Medicine] 1997, Vol. 36, pp. 300-303. Thus, one of skill in the art would be forced into first determining if, and at what dose, the chemotherapeutic agents causes apoptosis in the patient by assaying for morphological characteristics consistent with apoptosis before it could be determined if any of TGF-beta, p21, p16 or p27 were increased as a result of the chemotherapeutic agent. It is noted that for a marker associated only with senescence or terminal differentiation, the timing of the assay would not be as critical because the terminally differentiated or senescent cell would not be destined for disintegration or attack by a phagocytic cell.

Cohen et al (Biochemical Society Symposium, 1998, Vol. 63, pp. 199-210) teach that activation of Her-3 results in an increase in p21 nuclear staining. However, the abstract of Bacus et al (Proc Annu Meet Am Assoc Cancer Res, 1996, Vol. 37, A3945) teaches that the induction of p21 in breast cancer cell lines in response to doxorubicin fails to occur in cell expressing mutated or dominant negative p53. This is corroborated by Chang et al (Oncogene, 1999, Vol. Vol. 18, pp. 4808-4818, reference of the IDS filed November 19, 2002), who teach that doxorubicin treatment of a tumor cell line resulted in induction of increased levels of p21 which was completely confounded by the same cells transfected with a dominant negative p53 gene (page 4811, lines 19-29). Thus, one of skill in the art would be forced to determine if the cells taken from a patient exhibit mutated or dominant negative p53, and if said cells could be made to undergo apoptosis after treatment of said individual with a chemotherapeutic agent, followed by

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determining which of any of the remaining TGF-beta, p16 or p27 would function in said apoptotic cells.

Chang et al (Cancer Research, 1999, Vol. 59, pp. 3761-3767) teach that the chemotherapeutic induction of a senescence-like phenotype versus the induction of cell death in human tumor cell lines are independent processes. Chang et al teach that the overall outcome of exposure of chemotherapeutic agents is determined by a combination of factors responsible for the independent induction of cell death versus the senescence-like terminal differentiation such as the amount and the duration of exposure to the chemotherapeutic agent. Chang et al teach that the most common outcome of the treatment of human tumor cell lines is the induction of a senescence-like phenotype and mitotic cell death which contrasts with than apoptosis (page 3766, second column, first full paragraph).

Eymin et al (Oncogene, 1999, Vol. 18, pp. 1411-1418) teach that over expression of p27 is indicative of drug resistance in leukemic cells. Thus, if a sample of tissues or cells was taken from a leukemic patient after the administration of an apoptotic agent and an increase in p27 were noted, was of skill in the art would be forced to determine by other means if the increased expression of p27 were indicative of apoptosis, senescence or terminal differentiation, or if the increase in p27 were indicating that a selection of drug-resistance leukemia cells was made in said patient by the exposure to the chemotherapeutic agent.

It is concluded that given the breath of the claims to encompass any sample of tissue of cells taken from an individual who has received a chemotherapeutic agent, and the lack of a correlation between the increased expression of p21, p27, p16 and TGF-beta as a marker for apoptotic cells and/or terminally differentiated cells and/or senescent cells from all the types of tissue and cells in combination with all types and doses of chemotherapy agents encompassed by the method, one of skill in the art would be subject to undue experimentation in order to practice the broadly claimed method.

(B)As drawn to a chemopreventative agent

The instant claimed methods are reliant in part upon chemopreventative agents. When given the broadest reasonable interpretation, the term "chemopreventative" agents requires agents which prevent a pathology of any kind in any cell type before said pathology is required in said cell. Nether the specification nor prior art teaches the administration of such a

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chemopreventative agent to an individual and the removal of cell or tissues from said individual for the determination of an increase in SA-B-gal, p21, p27, p16 or TGF-beta. It is recognized that the art terms "chemoprevention" as intervening at early stages of carcinogenesis to prevent the manifestation of clinically apparent signs or symptoms of cancer, such as the effect of retinoids on early cancer lesions (Dragnev et al, The Oncologist, 2000, Vol. 5, pp. 361-368). However, the induction of terminal differentiation, apoptosis or senescence by retinoids does not fulfill the broad interpretation of the term "chemopreventative agent" which would require the prevention of any cancer, even an early neoplastic lesion. Given the lack of teaching in the specification and the prior art, one of skill in the art would be forced into undue experimentation in order to practice the claimed method on the evaluation of a response of an individual to a chemopreventative agent, because one of skill in the art would not know how to make such an agent.

The claims are drawn in part to method reliant on obtaining cells or tissue samples from an individual after exposure to a chemopreventative agent. When given the broadest reasonable interpretation, the claims encompass agents which prevent any type of pathology, such as infectious disease, autoimmune disease, genetically inherited disease and cancer in any cell or tissue type.

(C) As drawn to the requirement for an antibody which specifically binds to SA-B-gal

Claims 1, 2 and 4-6 are methods requiring an antibody which binds to SA-B-gal. The specification teaches measurement of SA-B-gal by detecting the blue color formed upon reaction of said antibody with X-gal. The art teaches that B-gal activity at pH 6 is indicative of senescence in cells, but that most cells express a B-gal activity at pH 4 (Dimiri et al, PNAS, 1995, Vol. 92, pp. 9363-9367, page 9364, first column, lines 11-17, under the heading "Results"). The specification does not contemplate the measurement of levels of SA-B-gal by means of an antibody, nor does it provide the structure of the SA-B gal, or a partial structure of the SA-B-gal that would allow one of skill in the art to make an antibody which would stain cells expressing SA-B-gal (pH 6 B-gal) but which would not stain the lysosomal B-gal. In order to practice the instant method one of skill in the art would be required to make and screen for anti-B-gal antibodies having the proper specificity which would not cross react with lysosomal B-gal. However, neither the specification nor the prior art have provided an amino acid sequence for

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SA-B-gal, and there are no teaching regarding the structural differences between the two enzymes which would give a reasonable expectation of success for the development of an antibody which would differentiate between the two types of B-gal. Because of the lack of teachings in the specification regarding these issues, one of skill in the art would be subject to undue experimentation in order to practice the broadly claimed invention.

5. All other rejections and objections as set forth or maintained in the previous Office action are withdrawn in light of applicants amendments.


6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.

9/19/2005


KAREN A. CANELLA PH.D.
PRIMARY EXAMINER